

Ann Rheum Dis 2001;60(Suppl 3):iii2-iii5 (November)

Consensus statement

Updated consensus statement on tumour necrosis factor blocking agents for the treatment of rheumatoid arthritis and other rheumatic diseases (April 2001)

As last year, the consensus group to consider the use of tumour necrosis factor (TNF) blocking agents was formed by an organising committee comprising rheumatologists from the universities of Erlangen, Leiden, and Vienna in Europe in cooperation with universities in the United States. Pharmaceutical support was obtained from a number of companies, but these institutions had no part in the decisions about the specific programme nor with regard to the participants or attendees at this conference.

The 148 rheumatologists and bioscientists from 21 countries who attended the consensus conference were chosen from a worldwide group of people felt to have experience or interest in the use of TNF blocking treatment for rheumatoid arthritis (RA) and other rheumatic diseases. Unfortunately, the number of attendees and participants was limited so that not everyone who might have been appropriate could be invited.

Additional information has come to light in the past year, both corroborating the major positive effect these drugs have had in RA and reporting possible new and unexpected adverse events. Therefore an update of the previous consensus statement seems both appropriate and necessary (Ann Rheum Dis 2000;59(suppl 1):i1-2).

In this update the consensus statement is annotated to document the credibility of the data supporting it, as far as possible. This annotation is that of Shekelle *et al* and is described in appendix 1.¹ All participants reviewed relevant clinical published articles relating to the TNF blocking agents. They were given a draft consensus statement and were asked to revise the document; open discussion of the revisions led to a final document, representing this updated consensus statement.

TNF blocking agents differ in composition, precise mechanisms of action, pharmacokinetics, biopharmaceutical properties, etc, but this document emphasises areas of commonality. Data which clearly differentiate compounds will be discussed, if such areas exist.

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Indications

Individual patients differ in the aggressiveness of their disease and its concomitant structural damage, the effect of their disease on their quality of life, and the symptoms and signs engendered by their disease. All these factors must be examined when considering anti-TNF treatment for the patient, as must the toxicity of previous and/or alternative disease modifying antirheumatic drug (DMARD) use.

TNF blockers are recommended for the treatment of active RA after an adequate trial of another effective DMARD, of which methotrexate is a commonly used example²⁻¹⁶ (category A evidence). TNF blocking agents can be added to pre-existing treatment, or, when appropriate, may replace previous DMARDs⁷⁻¹⁶ (category A evidence). There is evidence that TNF blockers are effective for the treatment of RA in methotrexate naive patients²⁻⁹ (category A evidence). The use of TNF blocking agents as the first DMARD for the treatment of RA² (category A evidence) should, at present, be limited owing to considerations of long term safety and cost. However, patients in whom other DMARDs are relatively contraindicated may be considered for treatment with TNF blockers as the first DMARD (category D evidence).

At least one TNF blocking agent has been approved for juvenile idiopathic arthritis of the polyarticular type^{17 18} (category A evidence). TNF blocking agents have been shown to be efficacious in psoriatic arthritis and ankylosing spondylitis¹⁸⁻²² (category A evidence). There is no evidence that any one TNF blocking agent should be used before another one can be tried, just as there is no credible evidence that one TNF blocker is more effective than another (category B evidence).

TNF blocking agents are being evaluated in Wegener's granulomatosis, adult onset Still's disease, polymyositis, and systemic sclerosis²³⁻²⁶ (category C evidence). These compounds may have potential in these diseases and in other conditions, but more work is needed in all cases.

Pharmacoeconomic data and long term safety data may change the circumstances when TNF blocking agents will be started, added to, or replace other DMARDs.

Clinical use

TNF blocking agents, when given in adequate doses and sufficiently frequent dosing regimens, should lead to significant, documentable improvement in symptoms, signs, and/or laboratory parameters within 8-12 weeks²⁻¹⁵ (category A evidence). Neither the American College of Rheumatology (ACR) response criteria nor the disease activity score (DAS) should be used in clinical practice as the sole measure to monitor individual response (category B evidence). Estimations of individual response require a combination of clinical judgment and quantitative measures, including the above and other validated quantitative measures, such as visual analogue scales (VAS) or Likert scales of global response or pain by the patient or global response by the doctor, joint tenderness and/or swelling counts, and laboratory data. Any may be used and may be the most appropriate measures for individual patients (category B evidence). These measures of response should be followed and individually important responses should be seen within 8-12 weeks²⁻¹⁵ (category A evidence). If such improvement occurs, treatment should be continued. If patients show no response to these agents, they should be stopped^{8 27 28} (category B

evidence). In patients with an incomplete response, observations suggest that an increased dose or reduced dosing intervals may provide additional benefit. However, further study of this issue is required^{8 27 28} (category D evidence).

Data show that TNF blocking agents slow radiographic progression in RA^{11 28} (category A evidence). Although radiographic progression slows down in some patients without a clinical response, the long term clinical implications of these changes are unknown. Until the long term implications of slowing radiological damage are clear, radiological changes, alone, should not determine clinical decision-making.

Some patients have inadvertently become pregnant while being treated with TNF blocking agents and these pregnancies have resulted in the birth of normal infants (category D evidence). However, there are insufficient data to advise continuation of anti-TNF treatment if a patient becomes pregnant.

Rare cases of lupus-like disease have occurred in patients receiving TNF blocking agents, and treatment should be stopped if there is clinical evidence of a lupus-like syndrome^{9 12 29} (category C evidence). There is no evidence that patients with RA who had, or develop, positive antinuclear antibodies (ANA), anticardiolipin antibodies (aCL), and/or dsDNA are at increased risk for the development of drug-induced lupus^{2-5 7-12 18 29} (category C evidence).

Warnings

TNF blocking agents should not be started or should be discontinued when serious infections occur, including septic arthritis, infected prostheses, acute abscess, osteomyelitis, sepsis, systemic fungal infections, *Listeria*, etc²⁻¹⁸ (category B evidence). Previous tuberculosis may be reactivated in patients given TNF blockers; screening and prophylaxis according to local recommendations should be undertaken in patients with previous tuberculosis or patients at risk for developing tuberculosis³⁰ (category C evidence). Treatment with TNF blockers in such patients should only be resumed if the infections have been adequately treated (category D evidence).

Instances of demyelinating-like disorders have been reported in patients receiving TNF blockers^{30 31} (category C evidence). These agents should be stopped if a demyelinating-like disorder occurs. Patients with a history of definite demyelinating disease should not receive TNF blocking agents (category C evidence).

A very few instances of pancytopenia and aplastic anaemia have been reported^{30 31} (category C evidence). Because the incidence of these adverse effects is not known, specific recommendations about monitoring cannot be given at this time. If pancytopenia or aplastic anaemia, or both, occur, TNF blockers should be stopped and patients evaluated for evidence of other underlying disease and a potential relationship with the TNF blockade (category C evidence).

Precautionary statements

The safety of TNF blockade is unknown or has not been established in the following situations:

- 1 Lymphoma, lymphoproliferative disease, and other malignancies
- 2 Chronic infections, including HIV, hepatitis B or C, etc
- 3 During pregnancy or lactation
- 4 When considering primary vaccinations or live attenuated vaccines.

Other areas in which knowledge is lacking are highlighted in the recommendations of the consensus group for areas most urgently requiring further research.

Research

Among a number of potential areas requiring action or further research, or both, the consensus groups felt the following projects or directions were most important in each of three areas: registries, efficacy, and safety.

REGISTRY

- 1 Long term registries have been developed to monitor efficacy and toxicity of TNF blocking agents and should continue, with cooperative efforts between payers, government, industry, and rheumatologists.
- 2 Registries of pregnancy outcomes for patients receiving anti-TNF therapy (and after cessation of treatment) should be continued.
- 3 What standards are required for long term trials and observational studies of TNF blockers? What are the outcomes of such studies in control subjects not taking TNF blockers?

EFFICACY

- 1 Are there predictors of response and toxicity for TNF blocking agents?
- 2 What are the optimal dosing regimens when using TNF blocking agents?
- 3 Is there a correlation between radiological effect and long term effectiveness for TNF blocking agents?

SAFETY

- 1 Can patients with evidence of previously treated mycobacterial infection, or fungal infection, use TNF blocking agents with safety in comparison with patients without such a history?
- 2 Can TNF blocking agents be used safely in pregnant or lactating women?
- 3 Do TNF blocking agents affect the efficacy of primary vaccination or the safety of live attenuated vaccination?
- 4 What is the safety profile of TNF blocking agents during surgery? How does it compare with the safety profile of patients undergoing surgery without concomitant TNF blocker use?

Summary

TNF blocking agents have proved to be effective DMARDs and they have been a major advance in the treatment of RA.²⁻¹⁷ Their use is expanding to other rheumatic diseases.^{18-26 32} However, rare to uncommon and unexpected toxicities have been found and others may yet be found during their use.

Studies in selected areas of efficacy, toxicity, and general use of TNF blocking agents are needed to help further define the most appropriate use of these agents. Use of these drugs will require doctors experienced in the diagnosis, treatment, and assessment of RA and other rheumatic diseases. These doctors will need to make long term observations of efficacy and toxicity. Further considerations which must be made when using TNF blocking agents in this disease include the cost and a recognition that data in subgroups are still being acquired. It is hoped that this statement, which is based upon the best evidence available at the time of its creation, and modified by expert opinion, will facilitate the optimal use of these agents for our patients with RA and other rheumatic diseases.

Appendix 1

- Category A evidence: based on evidence from at least one randomised controlled trial or on the meta-analyses of randomised controlled trials.
- Category B evidence: based on evidence from at least one controlled trial without randomisation or at least one other type of experimental study or on extrapolated recommendations from randomised controlled trials or meta-analyses.
- Category C evidence: based on non-experimental descriptive studies, such as comparative studies, correlational studies, and case-control studies or on extrapolated recommendations from randomised controlled trials, non-randomised controlled studies, or other experimental studies.
- Category D evidence: based on expert committee reports or opinions or clinical experience of respected authorities, or both, or on extrapolated recommendations from randomised controlled trials, meta-analyses, non-randomised controlled trials, experimental studies, or non-experimental descriptive studies.

Appendix 2: Summary of the "Updated consensus statement on TNF blocking agents for the treatment of RA and other rheumatic diseases"

INDICATIONS

- Individual patients differ in many aspects of their disease so one must frequently individualise treatment.
- TNF blockers are recommended for the treatment of active RA after using another DMARD (methotrexate is the most common of several DMARDs frequently used).
- TNF blocking agents can be added to pre-existing treatment or, when appropriate, may replace a previous DMARD.
- TNF blockers are effective in methotrexate naive patients.
- At present, TNF blocking agents as the first DMARD for the treatment of RA should be limited owing to considerations of long term safety and cost.
- In patients where other DMARDs are relatively contraindicated, TNF blockers may be considered as the first DMARD.
- At least one TNF blocking agent has been approved for juvenile idiopathic arthritis of the polyarticular type.
- TNF blockers are efficacious in psoriatic arthritis and ankylosing spondylitis.

- There is no evidence that any one TNF blocking agent should be used before another or that any TNF blocker is more effective than another, though individual differences may exist between patients.
- TNF blocking agents are being evaluated in Wegener's granulomatosis, adult onset Still's disease, polymyositis, systemic sclerosis, and other conditions, though more work is needed in all cases.
- Pharmacoeconomic data and long term safety may change all of the above statements.

CLINICAL USE

- When used in adequate doses and sufficiently frequent dosing regimens, TNF blocking agents should lead to significant, documentable improvement within 8-12 weeks.
- The ACR response criteria or DAS should not be used alone to monitor individual response; other validated quantitative measures such as VAS, Likert scales, joint tenderness and/or swelling, and laboratory data may be more appropriate measures for individual patients.
- If documentable significant improvement occurs, treatment should be continued.
- If patients show no response, these agents should be stopped.
- If an incomplete response occurs, increased doses or reduced dosing intervals may provide additional benefits, though further study of this issue is required.
- TNF blocking agents slow radiographic progression in RA. Until the long term implications of this slowing are clear, radiological changes alone should not determine clinical decision-making.
- Insufficient data are available about the use of anti-TNF therapy during pregnancy to allow advice in this circumstance.
- In the rare cases when lupus-like symptoms develop, TNF blocking agents should be stopped.
- The presence or development of a positive ANA, aCL, and/or dsDNA does not increase the risk of developing drug-induced lupus.

WARNINGS

- TNF blocking agents should not be started or should be discontinued when serious infections occur.
- Previous tuberculosis may be reactivated in patients given TNF blockers; screening and prophylaxis according to local recommendations should be undertaken in patients with previous tuberculosis or patients at high risk for developing tuberculosis.
- Instances of demyelinating-like disorders have been reported in patients receiving TNF blockers. These agents should be stopped if a demyelinating-like disorder occurs.
- Patients with a history of definite demyelinating disease should not receive TNF blocking agents.
- A very few instances of pancytopenia and aplastic anaemia have been reported, though the relationship and frequency of this adverse event is not sufficiently understood to make specific recommendations about monitoring at this time.
- If pancytopenia or aplastic anaemia occurs, TNF blockers should be stopped and patients evaluated for evidence of other underlying disease.

PRECAUTIONARY STATEMENT

- The safety of TNF blockade is unknown in the following situations: lymphomas and similar illnesses; chronic infections, including HIV and chronic hepatitis; during pregnancy or lactation;

when considering primary vaccinations or live attenuated vaccines.

- Research: a large number of research questions still need to be answered, but the reader is referred to the full consensus document for those research questions.

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Updated consensus statement on biological agents for the treatment of rheumatoid arthritis and other rheumatic diseases (May 2002)

Ann. Rheum. Dis, November 1, 2002; 61(90002): ii2 - 7.

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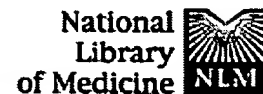
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Ann Rheum Dis, October 1, 2002; 61(10): 870 - 876.

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Anti-tumor necrosis factor-alpha monoclonal antibody therapy in severe alcoholic hepatitis.

Tilg H, Jalan R, Kaser A, Davies NA, Offner FA, Hodges SJ, Ludwiczek O, Shawcross D, Zoller H, Alisa A, Mookerjee RP, Graziadei I, Datz C, Trauner M, Schuppan D, Obrist P, Vogel W, Williams R.

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BACKGROUND/AIMS: Severe alcoholic hepatitis (AH) is associated with high mortality. Tumor necrosis factor-alpha (TNFalpha) has been demonstrated to play an important role in its pathophysiology. **METHODS:** Twelve patients with biopsy-confirmed AH and a Maddrey discriminant factor >32 were treated with a single infusion of the anti-TNF monoclonal antibody Infliximab at a dose of 5mg/kg body weight. Serial measurements were made for various cytokines using specific enzyme-linked immunoassays (ELISA). In four patients, liver biopsy samples were available pretreatment and on day+28 of therapy. **RESULTS:** Ten of the 12 patients are alive at a median of 15 (12-20) months. Two patients died within 30 days from septicemia. Serum bilirubin levels, Maddrey score, neutrophil count and C-reactive protein fell significantly within the first month. There was an early, though not significant, decrease in plasma levels of proinflammatory cytokines (interleukins (IL)-1beta, IL-6, IL-8, interferon-gamma), whereas plasma levels of TNFalpha remained near the sensitivity limit of the assay throughout the treatment course. While TNFalpha mRNA expression in the liver did not change, expression of IL-8, a cytokine regulated mainly by TNFalpha, was almost absent on day+28. **CONCLUSIONS:** Our data suggest that randomized controlled trials of anti-TNF antibody in severe AH are warranted.

PMID: 12663232 [PubMed - in process]

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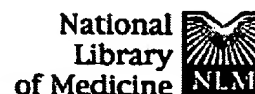
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Soluble tumor necrosis factor receptors in chronic hepatitis C: a correlation with histological fibrosis and activity.

Zylberberg H, Rimaniol AC, Pol S, Masson A, De Groote D, Berthelot P, Bach JF, Brechot C, Zavala F.

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BACKGROUND/AIMS: Tumor necrosis factor-alpha (TNF) is a mediator of inflammation and cellular immune response. Soluble TNF receptors (sTNFR) sTNF-R55 and sTNF-R75, which compete with cellular receptors for the binding of TNF, have been detected at high levels in infectious diseases including human immunodeficiency virus and HBV infection. In order to investigate the activation of the TNF system in HCV infection, we have analyzed the balance between TNF and sTNF-R in 60 HCV-infected subjects according to their clinical, biological, virological and histological characteristics. **METHODS:** Serum TNF, sTNF-R55 and sTNF-R75 levels were determined by ELISA before any therapy and were compared to a control group of 60 healthy subjects and a group of 34 HBV-infected patients. **RESULTS:** Mean TNF levels were 50.5 +/- 4.5 pg/ml in HCV patients, and undetectable (<5 pg/ml) in the control subjects. sTNF-R55 and sTNF-R75 levels were significantly higher in HCV-infected patients than in the controls: 2.88 +/- 0.14 ng/ml vs. 1.30 +/- 0.05, (p = 0.0001), and 9.54 +/- 0.58 ng/ml vs. 4.19 +/- 0.16, (p = 0.0001), respectively. sTNF-R55 and TNF-alpha levels in HCV patients were not significantly different from levels in HBV patients. sTNF-R75 levels were slightly lower than in HBV patients (9.54 +/- 0.58 vs. 11.4 +/- 0.79 ng/ml, p = 0.03). In contrast to other infectious diseases, there was no correlation between levels of sTNF-R and TNF. sTNF-R75 but not TNF levels were correlated with aminotransferases levels (p = 0.0001 and p = 0.0015 for aspartate and alanine aminotransferase, respectively), while sTNF-R55 levels were significantly correlated only with aspartate aminotransferase levels (p = 0.003). sTNF-R75 levels were significantly correlated with the Metavir activity index (p = 0.01), and sTNF-R55 and sTNF-R75 levels were significantly higher in patients with vs. without cirrhosis (3.22 +/- 0.21 vs. 2.54 +/- 0.17 ng/ml (p < 0.02) and 11.6 +/- 0.86 vs. 7.5 +/- 0.53 ng/ml (p < 0.001), respectively). sTNF-R55, sTNF-R75 and TNF levels were not correlated with viral load, genotype or response to interferon therapy. **CONCLUSIONS:** Levels of soluble TNF

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5 TNF-R55
45

receptors, and particularly sTNF-R75, are significantly correlated with the severity of the disease but not with virological parameters such as quantitative viremia and genotype. High TNF-R production could thus suggest that HCV-related liver disease involves immunological mechanisms, including activation of the TNF system.

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Disclosure:

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SAFETY OF TNF- α ANTAGONISTS IN PATIENTS WITH RHEUMATOID ARTHRITIS AND CHRONIC HEPATITIS C. Jeff R Peterson, Mark H Wener, Florence C Hsu, Peter A Simkin, Seattle, WA

Objective: To determine the effects of TNF- α antagonists on viral load and liver function in RA patients with chronic hepatitis C.

Methods: By a survey of community rheumatologists, we attempted to identify all patients with RA and chronic hepatitis C virus (HCV) who had received TNF- α antagonists. To date, 12 patients (10 etanercept, 2 infliximab) have been identified with adequate data for a retrospective examination of liver function tests (LFT's: albumin, alk phos, AST, ALT) and HCV viral load (quantitative PCR). LFT data were converted to percentage of upper limit of normal for each laboratory to allow for comparison. HCV quantitative changes were expressed as a ratio of the logs of the final over the initial viral loads.

Results: Nine patients had viral load measures by PCR at initiation of therapy and at varying times afterward from 1 to 14 months. The geometric mean of the log ratio of viral loads was 0.97 (range 0.79-1.14). At initiation of therapy, only one patient had LFT (AST, ALT) values greater than 2 times the upper limit of normal. None of the differences between LFT's at baseline vs 3 months or 12 months achieved statistical significance ($p > 0.05$ by paired T-test). The data below are expressed as the mean percent of the upper limit of normal \pm SD (median).

	albumin	alk phos	AST	ALT
Baseline (n=12)	73 \pm 9 (76)	95 \pm 100 (69)	109 \pm 109 (74)	112 \pm 100 (83)
3 months (n=12)	74 \pm (75)	74 \pm 42 (62)	106 \pm 73 (80)	117 \pm 83 (88)
12 months (n=4)	79 \pm 10 (83)	47 \pm 54 (45)	120 \pm 54(103)	150 \pm >137 (88)

Conclusion: This small retrospective study suggests that LFT and HCV viral load measurements are usually not affected by short-term use of TNF- α antagonists. Although long-term data are not yet available, these data suggest that TNF- α blockade can be considered in RA patients with chronic, stable hepatitis C. A prospective study is currently underway.

Disclosure:

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Ann Rheum Dis 2000;59(Suppl 1):i1-i2 (November)

Consensus statement

**Updated consensus statement on
tumour necrosis factor blocking agents
for the treatment of rheumatoid
arthritis (May 2000)**

As last year, a consensus group to consider the use of tumour necrosis factor (TNF) blocking agents was formed by an organising committee constituted of rheumatologists from the Universities of Erlangen, Leiden and Vienna in Europe in cooperation with universities in the United States.

Pharmaceutical support was obtained from a number of companies, but these institutions had no part in the decisions regarding this specific programme nor with regard to the participants or attendees at this conference.

The approximately 100 rheumatologists and bioscientists from 25 countries who attended the consensus conference were chosen from a worldwide group of people felt to have experience or interest in the use of TNF blocking treatment for rheumatoid arthritis (RA). Unfortunately, the number of attendees and participants were limited so that not everyone who might have been appropriate could be invited.

During the past year increasing amounts of data on the use of TNF blocking agents in RA have been published. Consequently it was felt appropriate to update the provisional consensus statement published last year (Ann Rheum Dis 1999;58 (suppl 1):I129-30).

During this revision it became clear that there are still large areas where knowledge is lacking. In an effort to clarify, for the readers, evidence on which the consensus statement is based, statements with supporting data have been referenced.

When a statement is not referenced it will have arisen from the consensus process: small group discussions, large group discussions and repeated drafts of the consensus statement to allow input from all participants. We feel that this statement represents an updated, although still provisional, consensus view of the use of TNF blockade in RA. However, it will require continued updating, and upgrading, as more evidence is gathered, presented in scientific forums and discussed.

While all TNF blocking agents are not alike (they differ in composition, precise mechanisms of action, pharmacokinetics, biopharmaceutical properties, etc) this consensus statement will emphasise areas of

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commonality and areas where knowledge is missing.^{1 2} If, and when, data differentiating compounds require discussion, they will be considered in the future, based on the persuasiveness of the data and the degree of difference demonstrated.

To help the reader understand the differences between last year's and this year's consensus statements, significant changes will be highlighted. Some statements have been altered to aid the flow or logic of the consensus statement, although their content and sense remains unchanged. Those statements will not be highlighted. Some statements have been dropped out. Those will not be noted in the present statement. Readers are urged to compare the two statements if they are interested in the latter.

Finally, to help point the way forward, the participants have presented areas where research is needed to help rheumatologists understand and use TNF blocking agents more rationally and effectively.

Indications

TNF blocking agents should normally be used for the treatment of active RA or juvenile chronic arthritis (JCA) after a full trial of an effective DMARD—of which methotrexate is a commonly used example—has been shown to be inadequate.³⁻⁵ Individual patients differ in the aggressiveness of their disease and its concomitant structural damage, the effect of their disease on their quality of life and the symptoms and signs engendered by their disease. All these factors must be examined when considering TNF treatment for that patient, as must the toxicity of previous DMARD use. TNF blocking agents can be added to pre-existing treatment or, when appropriate, may replace previous DMARDs.^{4 5} Initial controlled studies have shown that these agents are efficacious in rheumatoid arthritis (RA) before the use of conventional DMARDS.⁶ Pharmacoeconomic data and long term safety data may change the circumstances when TNF blocking agents will be started, added to, or replace other DMARDS (studies in progress).

Reasons for discontinuation

TNF blocking agents, when given in adequate doses and sufficiently frequent dosing regimens, should lead to significant, documentable improvement in symptoms, signs and/or laboratory parameters within 4-16 weeks.³⁻⁷ Quantifiable disease activity measures (such as tender and swollen joint counts, modified Health Assessment Questionnaires (HAQ), Visual Analogue Scales (VAS) for global response by patient or physician, VAS for pain, laboratory data or combined parameters of response) should be followed and a substantial response to treatment must be demonstrated in that time frame.¹⁻⁷ If such improvement has not occurred within that time frame, alternative treatments or regimens should be considered. Although there are data supporting the slowing of radiological progression of TNF blocking agents, the implication as well as clinical significance of this finding remains to be determined and requires further studies.⁶⁻⁸ Until such additional studies are completed radiological changes alone are insufficient by themselves to drive clinical decision making.

Warnings

TNF blocking agents should not be started or should be discontinued when serious infections occur, such as septic arthritis, infected prosthesis, pneumonia, pyelonephritis, acute abscesses, osteomyelitis, sepsis, systemic fungal infections, listeria or mycobacterial infections, etc.^{9 10} Treatment should only be resumed if such infections have been completely resolved and the risk of recurrence is low.

Precautionary statements

The effect of TNF blockade is unknown in the following situations:

- Lymphoma, lymphoproliferative and other malignancies.
- Chronic infections, including HIV, hepatitis B or C, mycobacterial disease, etc.
- During pregnancy or lactation.
- When considering primary vaccinations or live attenuated vaccines.

Other areas where knowledge is lacking are highlighted in the consensus groups recommendations for areas most urgently requiring further research.

Additional comments

Rare cases of lupus-like disease have occurred in patients receiving TNF blocking agents and treatment should be stopped if there is clinical evidence of drug induced lupus-like syndrome. There is thus far no evidence that RA patients who have positive ANA and/or ACL are at increased risk for the development of drug induced lupus.

If TNF blocking agents are proved efficacious and their safety and toxicity profile is demonstrated in patients with polyarticular psoriatic arthritis and ankylosing spondylitis and are approved by appropriate regulatory agencies these treatments could be used to treat those patients.¹¹

Among a number of potential areas requiring action and/or further research the consensus group felt the following projects or directions were most important in each of three areas: efficacy, toxicity and general issues:

EFFICACY

- What are the optimum dosing regimens and dosage intervals when using TNF blocking agents; also is intermittent use appropriate?
- Are there predictors of response (and toxicity), or lack thereof, for TNF blocking agents?
- Is there a correlation between radiological effect and long term effectiveness for TNF blocking agents?
- What are the clinically useful outcome measures to monitor anti-TNF administration?
- How does previous or concomitant DMARD treatment affect the efficacy and toxicity of TNF blocking agents?

TOXICITY

- A long term registry to monitor the toxicity and effectiveness of TNF blocking treatment is strongly recommended, requiring a cooperative effort among payors, government, industry and rheumatologists.
- Can patients with evidence of prior mycobacterial infection, or fungal infection, use TNF blocking agents with safety comparable to patients without such a prior history?
- Can TNF blocking agents be used in pregnant or lactating women (and their offspring) as safely as in matched female patients who are not pregnant or lactating?
- Do TNF blocking agents affect the efficacy of primary vaccination or the safety or effects of live attenuated vaccination?
- What is the safety profile of TNF blocking agents during surgery and how does it compare with the safety profile in patients undergoing surgery without concomitant TNF blocker use?

GENERAL USE

There is a need to develop and introduce an instrument that measures and documents quality management in the care of RA patients.

Summary

TNF blocking agents are promising therapeutic agents for RA. Studies in selected areas of efficacy, toxicity and the general use of TNF blocking agents are needed to help further define the most appropriate use of these agents. The use of these new agents will require physicians experienced in the diagnosis, treatment and assessment of RA. These physicians will need to make long term observations for efficacy and safety. Further considerations when using TNF blocking agents in this disease must include cost issues and recognition that data in subpopulations are still being acquired. It is hoped that this statement, which is based upon the best evidence available at the time of its creation and modified by expert opinion, will facilitate the optimal use of these agents for our patients with RA.

D E FURST, F C BREEDVELD, G R BURMESTER, J J CROFFORD, P EMERY, M FELDMANN, J R KALDEN, A F KAVANAUGH, E C KEYSTONE, L G KLARESKOG, P E LIPSKY, R N MAINI, A S RUSSELL, D L SCOTT, J S SMOLEN, L B A VAN DE PUTTE, T L VISHER, M H WEISMAN

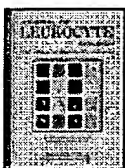
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CONSENSUS STATEMENT

Updated consensus statement on biological agents for the treatment of rheumatoid arthritis and other rheumatic diseases (May 2002)

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 C E Antoni⁵, J W J Bijlsma⁶, G R Burmester⁷,
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Keywords: tumour necrosis factor α ; blocking agents; rheumatoid arthritis; biological agents

Abbreviations: aCL, anticardiolipin antibody; ACR, American College of Rheumatology; ANA, antinuclear antibody; DAS, disease activity score; DMARD, disease modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire disease index; IL, interleukin; MTX, methotrexate; RA, rheumatoid arthritis; TNF, tumour necrosis factor; VAS, visual analogue scale

As in previous years, the consensus group to consider the use of biological agents was formed by an organising committee constituted of rheumatologists from the Universities of Erlangen, Leiden, and Vienna in Europe in cooperation with universities in the United States, Canada, and Europe.

Pharmaceutical industry support was obtained from a number of companies, but these institutions had no

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part in the decisions about the specific programme or about the academic participants at this conference.

The 158 rheumatologists and bioscientists from 22 countries who attended the consensus conference were chosen from a worldwide group of people felt to have experience or interest in the use of biological agents for the treatment of rheumatoid arthritis (RA) and other rheumatic diseases. Unfortunately, the number of attendees and participants was limited so that not everyone who might have been appropriate could be invited.

Additional information has come to light in the past year, both corroborating the major positive effect these drugs have had in RA and documenting possible new and unexpected adverse events. In addition, the first of a new class of targeted biological agents, interleukin 1 (IL1) blocking agents, has become available. Therefore an update of the previous consensus statement¹ seems both appropriate and necessary.

In the present update the consensus statement is annotated to document the credibility of the data supporting it as much as possible. This annotation is that of Shekelle *et al* and is described in appendix 3.² All participants reviewed relevant clinical published articles relating to tumour necrosis factor (TNF) and IL1 blocking agents. They were given a draft consensus statement and were asked to revise the document in small discussion groups; open discussion of the revisions led to a final document, representing this updated consensus statement.

General statements

Individual patients differ in the aggressiveness of their disease and its concomitant structural damage, the effect of their disease on their quality of life, and the symptoms and signs engendered by their disease. All these factors must be examined when considering biological treatment for the patient, as must the toxicity of previous and/or alternative disease modifying antirheumatic drug (DMARD) use.

In general, when measuring response to treatment, the American College of Rheumatology (ACR) response criteria (as a combined index) should not be used in clinical practice to monitor individual response (category B evidence).³ Validated quantitative measures such as the disease activity score (DAS), Health Assessment Questionnaire disease index (HAQ-DI), visual analogue scales (VAS) or Likert scales of global response or pain by the patient or global response by the doctor, joint tenderness and/or swelling counts, and laboratory data all may be used and may be the most appropriate measures for individual patients (category B evidence).³ The doctor should consider the patient's response using the above measures to determine the patient's status and improvement.

The use of these drugs will require doctors experienced in the diagnosis, treatment, and assessment of RA and other rheumatic diseases. These doctors will need to make long term observations for efficacy and toxicity.

Because these agents are not free from toxicity, patients or their representatives should be provided with information about potential risks and benefits so that they may give informed consent for treatment.

TNF BLOCKING AGENTS

TNF blocking agents differ in composition, precise mechanisms of action, pharmacokinetics, biopharmaceutical properties, etc, but this document emphasises areas of commonality. Data which clearly differentiate compounds will be discussed, if such areas exist.

Indications

TNF blockers are recommended for the treatment of active RA after an adequate trial of another effective DMARD, of which methotrexate (MTX) is a commonly used example (category A evidence).⁴⁻¹⁸ TNF blocking agents can be added to pre-existing treatment, or, when appropriate, may replace previous DMARDs (category A evidence).^{9-17,19} There is evidence that TNF blockers are effective for the treatment of RA in MTX-naïve patients (category A evidence).⁴⁻¹¹ The use of TNF blocking agents as the first DMARD for the treatment of RA (category A evidence)^{4,9-12} should, at present, be limited because these compounds are expensive and one needs to include cost considerations along with those of efficacy, effectiveness, and long term safety. However, patients in whom other DMARDs are relatively contraindicated may be considered for use of TNF blockers as the first DMARD (category D evidence).

One TNF blocking agent has been approved for juvenile idiopathic arthritis of the polyarticular type^{20,21} and for psoriatic arthritis²² (category A evidence). TNF blocking agents have been shown to be efficacious in ankylosing spondylitis and other spondyloarthropathies (category A evidence).²³⁻²⁶ A trial of TNF blocker treatment for adult onset Still's disease has been published (category B evidence).^{27,28} Anecdotal data have been published of its use in Behçet's uveitis and uveitis (category D evidence (letters)).^{29,30} It has also been used in Wegener's granulomatosis, Takayasu's arteritis, Sjögren's syndrome, polymyositis, systemic sclerosis, and giant cell arteritis (category D evidence (abstracts)).³¹⁻³³ These compounds may have potential in these and other conditions, although more work is needed in all cases.

Pharmacoeconomic data and long term safety data may change the circumstances when TNF blocking agents will be started.

Clinical use

TNF blocking agents, when given in adequate doses and sufficiently frequent dosing regimens, should lead to significant, documentable improvement in symptoms, signs and/or laboratory measures within 12 weeks (category A evidence).⁴⁻¹⁷ There is no evidence that any one TNF blocking agent should be used before another one can be tried, just as there is no credible evidence that any TNF blocker is more effective than another (category D evidence (abstracts)).³⁴⁻³⁹ Individually important responses, including patient oriented measures (for example, HAQ-DI, patient's global VAS) or physical measures (for example, joint tenderness), should be demonstrated within 8-12 weeks for RA (category A evidence).⁴⁻¹⁷ If such improvement occurs, treatment should be continued. If patients show no response to these agents, treatment should be stopped. In patients with an incomplete response, observations suggest that increasing the dose or reducing the dosing intervals may provide additional benefit, as may the addition or substitution of other DMARDs or other biological agents (category A evidence¹⁰;

category D evidence (abstracts)^{19,39}).

There are data showing that TNF blocking agents slow radiographic progression in RA^{13,35} (category A evidence¹³; category D evidence (abstract)³⁵). Although in some patients who have only partial clinical response, radiographic progression slows, the long term clinical implications of these changes are unknown. Until the long term implications of slowing radiological damage are clear, radiological changes alone should not determine clinical decision-making.

Some patients inadvertently become pregnant while being treated with TNF blocking therapy. Pharmacovigilance data show that the rate of normal live births, miscarriages, and therapeutic terminations is consistent with reported data for the general population (category D evidence (abstract)).⁴⁰ However there are insufficient data to advise continuation of anti-TNF therapy if a patient becomes pregnant.

Rare cases of lupus-like disease have occurred in patients receiving TNF blocking agents (all of whom were dsDNA positive), and treatment should be stopped if there is clinical evidence of a lupus-like syndrome (FDA)^{11,14,18,41} (category C evidence). There is no evidence that patients with RA who had, or develop, a positive antinuclear antibody (ANA), anticardiolipin antibody (aCL) and/or dsDNA are at increased risk for the development of drug induced lupus (FDA) (category C evidence (FDA)^{4-7,9-14,21}; category D evidence (abstracts)^{18,41}).

In clinical studies, injection site reactions and infusion reactions were more common in the treatment groups than the placebo groups (category A evidence).⁴⁻¹⁷

Warnings

TNF blocking agents should not be started, or should be discontinued, when serious infections occur, including septic arthritis, infected prostheses, acute abscess, osteomyelitis, sepsis, systemic fungal infections, *Listeria* etc. (FDA)^{4-17,21} (category B evidence). Treatment with TNF blockers in such patients should only be resumed if the infections have been treated adequately (category D evidence).

Previous tuberculosis may be reactivated in patients given TNF blockers; every patient should be evaluated, including a history and physical examination, for the possibility of latent tuberculosis, and treatment for the possibility of latent tuberculosis should be started according to local recommendations (category C evidence).⁴² Some authorities suggest that TNF blockers may be started as soon antituberculosis treatment is started, although this approach needs further investigation (category D evidence).

Instances of demyelinating-like disorders have been reported in patients receiving TNF blockers, although it is not known currently if the incidence in patients receiving TNF blockers is different from that of a comparable group of patients with RA not treated with TNF blocking agents (FDA)^{18,41,43} (category C evidence (FDA); category D evidence^{18,41,43}). These agents should be stopped if a demyelinating-like disorder occurs. Patients with a history of definite demyelinating disease should not receive TNF blocking agents. (category D evidence)

A very few instances of pancytopenia and aplastic anaemia have been reported (category C evidence).^{18,41} Because the incidence of these adverse effects is not known and their relative frequency compared with the general population is also not known, specific recommendations about monitoring cannot be given at this time. If pancytopenia and/or aplastic anaemia occur, TNF blockers should be stopped and patients evaluated for evidence of other underlying disease and potential relationship with the TNF blockade (category C evidence).

Patients with severe (NYHA class III or IV) congestive heart failure given TNF blockers may have an increased relative risk of worsening congestive heart failure and mortality, and each patient's risk versus benefit should be considered before the use of TNF blocking agents is begun or continued in those circumstances (FDA) (category C evidence).

The long term safety or efficacy of TNF blockers in patients with hepatitis C is not known. Controlled studies are awaited. A short, pilot study of TNF blockade in patients with hepatitis C showed no increased viral load over six months (category D evidence (abstract)).⁴⁴

Precautionary statements

The safety of TNF blockade is unknown or has not been established in the following situations:

1. Lymphoma, lymphoproliferative and other malignancies
- ✓ 2. Chronic infections, including HIV, hepatitis B etc
3. During lactation
4. When using IL1 blocking agents and TNF blocking agents together; infections are common and serious infections have occurred and this combination should be used with great caution until new data become available (category D evidence (abstract)).⁴⁵
5. When using live attenuated vaccines

Other areas where knowledge is lacking are highlighted in the consensus group's recommendations for areas most urgently requiring further research.

Research questions

Among a number of potential areas requiring action or further research, or both, the consensus groups felt the following projects or directions were most important in each of four areas: registries, efficacy, toxicity, and general issues.

Registry

1. Long term registries to monitor the toxicity of biological agents are strongly recommended, requiring a cooperative effort among payers, government, industry, and rheumatologists.
2. It would be appropriate to convene a workshop to create common standards for such registries and to have a forum for comparisons of results.
3. Registries of pregnancy outcomes in patients receiving anti-TNF therapy (and after therapy has ended) should be continued.

4. What standards are required for long term trials and observational studies of TNF blockers? What are the outcomes of such studies in relationship to control subjects not taking TNF blockers?

Efficacy

1. What are the optimal dosing regimens when using TNF blocking agents?
2. Can one switch from one TNF blocking agent to another with improved response and reduced toxicity (some abstracts indicate that switching seems to be effective for some patients)?
3. What is the effect of addition of DMARDs when there is only a partial response to a TNF blocking agent?
4. Can infliximab be used alone or with DMARDs other than MTX?
5. Are there predictors of response and toxicity for TNF blocking agents?
6. Is there a correlation between radiological effect and long term effectiveness for TNF blocking agents?
7. What are the outcomes of patients treated with TNF blocking agents in whom disease activity persists without joint destruction and where joint destruction is observed with little disease activity?
8. Can TNF blockers be used as induction therapies in conjunction with and continuation of traditional DMARDs?
9. Can biological agents be given at lower than currently used doses and/or at dosing intervals longer than currently used to slow or halt radiographic progression in the absence of an ACR20 response?

Safety

1. Can patients with evidence of prior treated mycobacterial infection, or fungal infection, use TNF blocking agents as safely as patients without such a history?
2. Can TNF blocking agents be used safely in pregnant or lactating women?
3. Do TNF blocking agents affect the efficacy of primary vaccination or the safety of live attenuated vaccination?
4. What is the safety profile of TNF blocking agents during surgery? How does it compare to the safety profile of patients undergoing surgery without concomitant TNF blocker use?

Summary

TNF blocking agents have proved to be effective DMARDs and are a major advance in the treatment of RA. Their use is expanding to other rheumatic diseases. However, rare to uncommon and unexpected toxicities have been found and others may yet be found during their use. Studies in selected areas of efficacy, toxicity, and general use of TNF blocking agents are needed to help define further the most appropriate use of these agents. Other considerations when using TNF blocking agents in this disease should balance efficacy, toxicity, and cost and recognise that data in subgroups of patients are still being acquired. It is hoped that this statement, which is based upon the best evidence available at the time of its creation and is modified by expert opinion, will facilitate the optimal use of these agents for our patients with RA.

IL1 BLOCKING AGENTS

To date only one IL1 blocking agent (Anakinra) has reached the market and references are therefore to this product. As other agents of this class reach the market, the document below will be changed appropriately, but it may appear somewhat inconsistent at present as attempts are made to separate presumed class characteristics from data relating to this prototypic compound.

Indications

IL1 blocking agents may be used for treatment of active RA, alone or with MTX (category A evidence).^{46,47} Despite this evidence, the Anakinra label presently requires its use with MTX in Europe. IL1 blocking agents are recommended for the treatment of active RA after an adequate trial of another effective DMARD, of which MTX is a common example (category D evidence). Anakinra has been used with other effective DMARDs (category D evidence (abstract)).⁴⁸

The use of IL1 blocking agents as the first DMARD for the treatment of RA should, at present, be limited because these compounds are expensive and one needs to include cost considerations along with those of efficacy, effectiveness, and long term safety (category D evidence).

Clinical use

IL1 blocking agents can lead to significant, documentable improvement in symptoms, signs, and/or laboratory parameters within 2–16 weeks (category A evidence).^{46,47,49} Measures of patient related outcomes such as the patient's global VAS or HAQ may be more sensitive to the effects of one IL1 blocking agent (Anakinra) than physical measures such as joint tenderness/swelling (category D evidence (abstract)).⁵⁰ These measures of response should be followed up and individually important responses should be demonstrated within 8–16 weeks (category A evidence).^{46,47,51} If clinically important improvement occurs, treatment should be continued (category D evidence).

There are data showing that IL1 blocking agents, of which Anakinra is the marketed prototypic compound, slows radiographic progression in rheumatoid arthritis (category A evidence).^{46,51}

Reactions at the injection site related to dose and affecting up to 70% of patients have occurred with the use of Anakinra. These reactions often do not require treatment and seem to moderate with continued use in some patients (category A evidence^{46,47,49}; category D evidence (abstract)⁴⁸).

There are no data to advise either termination or continuation of IL1 blocking agents if a patient becomes pregnant.

The efficacy and toxicity of IL1 blocking compounds in rheumatic diseases other than RA are unknown.

Warnings

Possibly, there is a small increased incidence of infections, including serious infections, when using IL1 blocking compounds. Therefore, these compounds should not be started or should be discontinued when serious infections occur^{45–47,49} (category A evidence^{46,47,49,51}; category D evidence (abstract)⁴⁸).

Treatment with IL1 blocking therapy in such patients should only be resumed if the infections have been

adequately treated (category D evidence).

Precautionary statements

The safety of IL1 for use in RA is unknown or has not been established in the following situations:

1. Lymphoma, lymphoproliferative and other malignancies
2. During pregnancy or lactation, or both
3. When using IL1 blocking agents and TNF blocking agents together; in combination with other biological agents/targeted therapy, such as TNF blocking agents, infections are common and serious infections have occurred and this combination should be used with great caution until new data become available (category D evidence (abstract)⁴⁵)
4. When considering primary vaccinations or live attenuated vaccines

Other areas where knowledge is lacking are highlighted in the consensus group's recommendations for areas most urgently requiring further research.

Research

Among a number of potential areas requiring action and/or further research, the consensus groups felt the following projects or directions were most important in each of four areas: registries, efficacy, toxicity, and general issues.

Registry

1. Long term registries to monitor the toxicity of biological agents are strongly recommended, requiring a cooperative effort among payers, government, industry, and rheumatologists.
2. It would be appropriate to convene a workshop to create common standards for such registries and to have a forum for comparisons of results.
3. Registries of pregnancy outcomes in patients receiving IL1 blocking therapy (and after therapy has ended) should be continued.
4. What standards are required for long term trials and observational studies of IL1 blocking agents? What are the outcomes of such studies in relationship to control subjects not taking IL1-blockers?

Efficacy

1. What is the efficacy of IL1 blocking agents in patients who have used TNF blockers but have not responded or have not responded sufficiently?
2. What is the efficacy of IL1 blocking agents in polyarticular juvenile arthritis and other rheumatic diseases, including osteoarthritis?
3. Do TNF blocking agents have an effect on pain?

Toxicity

1. Can IL1 blocking agents be used in patients who cannot be treated with TNF blocking agents because they have a history of tuberculosis or latent tuberculosis and cannot tolerate appropriate

treatment for the latter, for some reason?

Summary

IL1 blocking agents, of which Anakinra is the prototypic and sole example, are effective for the treatment of RA but their specific place (for example, before, after, or with TNF blocking agents) in the rheumatological armamentarium is not yet defined. Publication of studies in selected areas of efficacy, toxicity, and general use of IL1 blocking agents are needed to help define further the most appropriate use of these agents. Further considerations when using IL1 receptor antagonists in this disease must include the cost and recognition that data in subgroups of patients are still being acquired. It is hoped that this statement, which is based upon the best evidence available at the time of its creation, and modified by expert opinion, will facilitate the optimal use of IL1 receptor antagonists for our patients with RA.

APPENDIX 1 ABBREVIATED SUMMARY OF THE "UPDATED CONSENSUS STATEMENT ON BIOLOGICAL AGENTS FOR THE TREATMENT OF RA AND OTHER RHEUMATIC DISEASES—TNF BLOCKING AGENTS SUBSECTION"

- Rheumatologists and bioscientists from numerous countries met to develop the consensus statement.
- A new consensus statement was required because additional information has corroborated the major positive effect of these drugs and possible new and unexpected adverse events have occurred.
- The process included a review of all relevant clinical published articles and, through an iterative process, the reaching of consensus.
- Individual patients differ in many aspects of their disease so one must frequently individualise treatment.
- TNF blocking agents differ in many ways, but this document emphasises areas of commonality, until clear differences can be shown among TNF blockers.

Indications

- TNF blockers are recommended for the treatment of active RA after using another DMARD (MTX is the most common of several DMARDs frequently used).
- TNF blocking agents can be added to pre-existing treatment or, when appropriate, may replace previous DMARDs or other biological agents.
- TNF blockers are effective in MTX-naïve patients.
- At present, TNF blocking agents as the first DMARD for the treatment of RA should be limited because of considerations of long term safety. The cost should be included when considering the use of TNF blocking agents.
- When other DMARDs are relatively contraindicated, TNF blockers may be considered as the first DMARD.
- One TNF blocking agent has been approved for juvenile idiopathic arthritis of the polyarticular

type as well as for psoriatic arthritis.

- TNF blockers are efficacious in ankylosing spondylitis.
- There is no evidence that any one TNF blocking agent should be used before another or that any TNF blocker is more effective than another, although individual differences may exist between patients.
- TNF blocking agents are being evaluated in Wegener's granulomatosis, giant cell arteritis, Takayasu arteritis, adult onset Still's disease, Sjögren's syndrome, hepatitis C, Behçet's disease, uveitis, polymyositis, systemic sclerosis, and other conditions, although more work is needed in all cases.
- Pharmacoeconomic and long term safety data may modify all of the above statements.

Clinical use

- When used in adequate doses and sufficiently frequent dosing regimens, TNF blocking agents should lead to significant, documentable improvement within 12 weeks for RA.
- The ACR response criteria (as a combined index) should not be used to monitor individual response; other validated quantitative measures such as the DAS, HAQ-DI, VAS, Likert scales, joint tenderness and/or swelling, and laboratory data may be more appropriate measures for individual patients.
- If documentable significant improvement occurs, treatment should be continued.
- If patients show no response to these agents treatment should be stopped.
- If an incomplete response occur, increased doses or reduced dosing intervals may provide additional benefits as may other DMARDs or other biological agents, although further study of this issue is required.
- TNF blocking agents slow radiographic progression in RA. Until the long term implications of this slowing are clear, radiological changes alone should not determine clinical decision-making.

Warnings

- Insufficient data are available about the use of anti-TNF therapy during pregnancy to allow advice in this circumstance, although pharmacovigilance data have shown the same rate of normal births, miscarriages, and therapeutic terminations as in the general population.
- In the rare cases when lupus-like symptoms develop, TNF blocking agents should be stopped.
- The presence or development of a positive ANA, aCL, and/or dsDNA does not increase the risk of developing drug-induced lupus.
- TNF blocking agents should not be started or should be discontinued when serious infections occur.
- Previous tuberculosis may be reactivated in patients given TNF blockers; individual evaluations, including history and physical examinations should be done and treatment for latent tuberculosis considered, according to local recommendations.
- When severe congestive heart failure is present TNF blockade should be used with caution.
- Instances of demyelinating-like disorders have been reported in patients receiving TNF blockers. These agents should be stopped if a demyelinating-like disorder occurs.

- Patients with a history of a definite demyelinating disease should not receive TNF blocking agents.
- A very few instances of pancytopenia and aplastic anaemia have been reported, although the relationship and incidence of this adverse event is not sufficiently understood to make specific recommendations about monitoring at this time.
- If pancytopenia or aplastic anaemia occurs, TNF blockers should be stopped in patients evaluated for evidence of other underlying disease.

Precautionary statements

- The safety of TNF blockade is unknown in the following situations: lymphomas and similar illnesses; chronic infections including HIV and chronic hepatitis; during pregnancy or lactation; when considering primary vaccinations or live attenuated vaccines.

APPENDIX 2 ABBREVIATED SUMMARY OF THE "UPDATED CONSENSUS STATEMENT FOR THE USE OF BIOLOGICAL AGENTS IN THE TREATMENT OF RA AND OTHER RHEUMATIC DISEASES—IL1 BLOCKING AGENTS SUBSECTION"

- Rheumatologists and bioscientists from numerous countries met to develop the consensus
- A new consensus statement was required because IL1 blocking agents are beginning to appear, and possible new and unexpected adverse effects have occurred.
- The process included a review of all relevant clinical published articles and, through an iterative process, the reaching of consensus.
- Biological agents may differ in many ways, although there is presently only one prototypic agent, Anakinra, representing the IL1 blocking agents.

Indications

- IL1 blocking agents may be used, alone or with MTX, for the treatment of active RA. In Europe, IL1 blocking agents (Anakinra) should presently be used in conjunction with MTX.
- IL1 blocking agents will probably be effective when used with other effective DMARDs.

Clinical use

- IL1 blocking agents (Anakinra) can lead to significant documentable improvement in symptoms, signs and/or laboratory measures within 2–16 weeks.
- Response measures should be followed up and individually important responses should be demonstrated within 8–16 weeks.
- If clinically important response to IL1 blocking agents occurs, the agent(s) should be continued.
- IL1 blocking agents (Anakinra) slow radiographic progression in RA.
- Reactions at injection site occur in up to 70% of patients in a dose-response manner. These injection site reactions often do not require treatment and may diminish with continued use.

- There are no data to advise continuation or termination of IL1 blocking therapy if the patient becomes pregnant.
- The efficacy and toxicity of IL1 blocking agents in rheumatic diseases other than RA are unknown.

Warnings

- Possibly, there is a small increased incidence of infections, including serious infections, when using IL1 blocking agents.
- IL1 blocking agents should not be started or should be discontinued when serious infections occur.
- Treatment with IL1 blocking agents should only be resumed if infections have been adequately treated.

Precautionary statements

- The safety of IL1 blocking agents is unknown or has not been established in the following situations: lymphoma, lymphoproliferative disease or other malignancies; pregnancy and/or lactation; in combination with other biological agents, including TNF blocking agents (where great care should be taken if these drugs are used together); when using primary vaccinations or live attenuated vaccines.

APPENDIX 3 EVIDENCE SCHEME

Category A evidence:

Based on evidence from at least one randomised controlled trial or on the meta-analyses of randomised controlled trials.

Category B evidence:

Based on evidence from at least one controlled trial without randomisation or at least one other type of experimental study or on extrapolated recommendations from randomised controlled trials or meta-analyses.

Category C evidence:

Based on non-experimental descriptive studies, such as comparative studies, correlational studies, and case-control studies, which are extrapolated from randomised controlled trials, non-randomised controlled studies, or other experimental studies.

Category D evidence:

Based on expert committee reports or opinions or clinical experience of respected authorities, or both, or on extrapolated recommendations from randomised controlled trials, meta-analyses, non-randomised controlled trials, experimental studies or non-experimental descriptive studies.

Note:

Abstracts have not been considered in the above evidence scheme, as they are not complete and may

change by the time the data are published, or may not be published as full papers at all. Evidence from abstracts alone, therefore, is considered as category D evidence and noted as "abstract" until those data are published as a complete, peer reviewed paper.

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